Mast Cell Disease and Its Diagnosis

Michael D. Tharp
Department of Dermatology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, U.S.A.

Mastocytosis or mast cell disease (MCD) represents a group of clinical disorders that result from the abnormal accumulation of mast cells in tissues, and conditions within the MCD spectrum vary in regard to their clinical manifestations and extent of organ involvement [1–4].

In general, the diagnosis of MCD often can be established at the time of the physical examination because most, but not all, patients have relatively characteristic cutaneous lesions. The bedside maneuver of gently stroking urticaria pigmentosum and telangiectasia macularis eruptiva perstans lesions usually results in a local wheal and flare reaction (Darier's sign) thereby substantiating the diagnosis [1–3]. Confirmation of cutaneous MCD is most readily accomplished by performing a biopsy of a characteristic lesion and demonstrating increased numbers of mast cells. Because methods for quantifying skin mast cells had yielded varying results, we combined the technique of morphometric point counting with the mast cell–specific fluorescein isothiocyanate–avidin stain to enumerate mast cells in normal skin and lesions of mastocytosis [5]. Using this approach, we observed that nodules, papules, and telangiectatic macules of MCD had approximately a 150-, 40-, and 9-fold increase in mast cell content, respectively, when compared to normal skin. Morphometric analysis of non-lesional skin biopsies from these same patients and from lesional skin of patients with disorders that might be confused with MCD such as urticaria, essential telangiectasis, and chronic eczema did not demonstrate significant increases in mast cells above controls. Taken together, these observations demonstrate that the diagnosis of MCD in the skin can be made on physical examination and confirmed by simple histologic techniques.

But what are the criteria for the diagnosis of systemic MCD? Systemic MCD is defined as an increase in the number of mast cells in organs other than the skin. Clinically there are some signs that may be helpful in establishing the diagnosis of systemic disease. Fifty percent or more of systemic MCD patients have hepatomegaly, splenomegaly, and/or lymphadenopathy on physical examination [1,6,7]. In addition, a number of these patients have bone involvement that often can be visualized on skeletal x-rays or radionucleotide bone scans [8,9]. More direct approaches also have been used to diagnose this systemic disorder. Increased numbers of mast cells have been reported in biopsies of liver and/or bone marrow from some mastocytosis patients; however, because of the invasiveness of these procedures and their associated morbidities, attempts have been made to correlate levels of circulating mast cell mediators with the extent of MCD [1,4,6,10–13].

Mast cells are known to produce pharmacologically potent molecules including histamine and prostaglandin D_2 (PGD_2), and the local and systemic release of these mediators contributes significantly to the spectrum of clinical signs and symptoms observed in MCD patients [1,3,4]. Elevations in urine and plasma histamine levels have been documented in some systemic MCD patients during or immediately following symptomatic episodes [1,3]. However, random urinary histamine determinations have not proved useful in the diagnosis of systemic MCD, because only 1–3% of this amine appears unmetabolized in the urine [10,11]. In contrast, the major urinary histamine metabolites, N^T-methylhistamine and 1-methyl-4-imidazoleacetic acid (MelmAA), are increased in patients with MCD and often are elevated in asymptomatic patients with systemic involvement [10,11]. Granerus *et al* have reported a direct correlation between urinary MelmAA levels and the extent of mast cell infiltration in the skin and other organs [10]. They noted the highest urinary excretion of MelmAA in patients with the most extensive disease. Elevated plasma levels of mast cell–derived tryptase also have been reported in some MCD patients; however, increased circulating levels of this mediator have been identified in patients without MCD who experienced anaphylaxis [12]. Increased urinary excretion of the major metabolite of PGD_2 (9-alpha,11-beta-dihydroxy-15-oxo-2,3,18,19-tetranor-prost-5-ene-1,20-dioicacid, PGD-M), also has been detected in patients with MCD. Initially, elevated levels of PGD-M were identified in a subgroup of MCD patients who experienced repeated episodes of flushing, hypotension, and syncope [13]. Interestingly, many of these patients lacked persistent cutaneous lesions. This same investigative group has pursued PGD-M as a possible diagnostic tool for MCD, and in this month's journal (p. 937), these authors have compared urinary levels of PGD-M to N^T-methylhistamine as indicators of mastocytosis. In this report, 17 MCD were studied, all of which had persistent cutaneous lesions, and 11 of 15 had increased numbers of bone-marrow mast cells. Twenty-four–hour urine sample collections showed elevated levels of PGD-M in 16 of 17 patients whereas increased N^T-methylhistamine concentrations were found in only 12. In most patients, the magnitude of increases above normal values was greater for PGD-M than N^T-methylhistamine, thus leading the authors to conclude that the measurement of urinary PGD-M is a more sensitive test for MCD than N^T-methyl-histamine.

Although the measurement of urinary histamine metabolites and PGD-M levels have some merit in the evaluation of patients with MCD, it is also important to recognize its limitations. For example, levels of urinary histamine and its metabolites can be affected by the dietary intake of histamine or histidine [10,11,14]. In addition, diseases such as polycythemia vera and chronic myelocytic leukemia have been associated with persistent increases in urinary histamine metabolites [11]. Although elevations in PGD-M have been demonstrated in patients with MCD, they also have been documented in the serum and urine of normal volunteers after the ingestion of niacin [15]. In addition, increased levels of PGD-M have been detected in a patient without MCD who experienced urticaria and bronchospasm, indicating that degranulation of normal numbers of mast cells in certain clinical situations is capable of causing elevated levels of this metabolite [15]. Even the direct enumeration of mast cells in the skin or bone marrow is not absolutely specific for MCD. Increased cutaneous mast cells have been reported in neurofibromas as well as several other skin tumors, and expanded bone-marrow mast cell populations have been associated with preleukemic, leukemic, and lymphoproliferative disorders [16,17].

What can be surmised from this information? First, it is important

0022-202X/95/$09.50 • SSDI0022-202X(95)00201-U

to emphasize that MCD is a spectrum with diverse clinical symptoms and signs; thus, it is likely that no single test would be absolutely diagnostic for this disease. Currently, the demonstration of increased mast cells in characteristic skin lesions comes the closest to a "gold standard" test for MCD. Second, the detection of increased mast cells in other tissues or the finding of elevated levels of mast cell mediators in the peripheral circulation or urine must always be interpreted in the context of the clinical situation. In certain patients suspected of having systemic MCD, but who lack typical signs of the disorder, one or more of these tests may be useful. In reference to the measurement of PGD-M, the present study suggests that this test is a sensitive indicator of mast cell degranulation. What is not certain, however, is whether it discriminates patients with MCD from those experiencing other forms of mast cell mediator release such as urticaria, asthma, and anaphylaxis. Additional studies comparing PGD-M levels in these two patient groups may be worthwhile, especially if significant differences can be demonstrated.

Recently, there have been some advances in understanding mast cell development and maturation. The cytokine stem cell factor (SCF) has been recognized for its importance in the growth of normal mast cells [18]. Increased expression of the soluble form of SCF has been reported in the skin of MCD patients, thus suggesting that the overproduction of this cytokine may play a role in this disorder [19]. Future studies examining SCF and the regulation of its synthesis may prove important in understanding the pathogenesis of MCD and may lead to the development of new and innovative treatments for this disorder.

REFERENCES

1. Sagher F, Even-Paz Z: *Mastocytosis and the Mast Cell.* Chicago, Yearbook Medical Publishers, 1967, pp 14–228
2. Caplan RM: The natural course urticaria pigmentosa. *Arch Dermatol* 87:146–157, 1963
3. Demis DJ: The mastocytosis syndrome: clinical and biological studies. *Ann Intern Med* 59:194–206, 1963
4. Roberts LJ, Sweetman BJ, Lewis RA, Austen KF, Oates JA: Increased production of prostaglandin D2 in patients with systemic mastocytosis. *N Engl J Med* 303:1400–1404, 1980
5. Kasper CS, Freeman RG, Tharp MD: Diagnosis of mastocytosis subsets using a morphometric point counting technique. *Arch Dermatol* 123:1017–1021, 1987
6. Webb TA, Li CY, Yam LT: Systemic mast cell disease: a clinical and hematopathologic study of 26 cases. *Cancer* 49:927–938, 1982
7. Travis WE, Li CY, Hoagland HC, Travis LB, Banks PM: Mast cell leukemia: report of a case and review of the literature. *Mayo Clin Proc* 61:957–966, 1986
8. Poppel MN, Gruber WF, Silber R, Holder AK, Christman RO: The roentgen manifestations of urticaria pigmentosa (mastocytosis). *Am J Radiat Roentgenol* 82:239–249, 1959
9. Rosenbaum RC, Frieri M, Metcalfe DD: Patterns of skeletal scintigraphy and their relationship to plasma and urinary histamine levels in systemic mastocytosis. *J Nucl Med* 25:859–864, 1984
10. Granerus G, Olafasson JH, Roupe G: Studies on histamine metabolism in mastocytosis. *J Invest Dermatol* 80:410–416, 1983
11. Keyzer JL, DeMonchy JGR, vanDoormaal JJ, van Voorst Vader PC: Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. *N Engl J Med* 309:1603–1605, 1983
12. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T: Tryptase levels as an indicator of mast cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med* 316:1622–1626, 1987
13. Roberts LJ, Fields JP, Oates JA: Mastocytosis without urticaria pigmentosa: a frequently unrecognized cause of recurrent syncope. *Trans Assoc Am Phys* 95:36–41, 1982
14. Feldman JM: Histaminuria from histamine-rich foods. *Arch Intern Med* 143:2099–2102, 1983
15. Awad JA, Morrow JD, Roberts LJ III: Detection of the major urinary metabolite of prostaglandin D2 in the circulation: demonstration of elevated levels in patients with disorders of systemic mast cell activation. *J Allergy Clin Immunol* 93:817–24, 1994
16. Cawley EP, Hoch-Ligeti C: Association of tissue mast cells and skin tumors. *Arch Dermatol* 83:146–150, 1961
17. Prokocimer M, Polliack A: Increased bone marrow mast cells in preleukemic syndromes, acute leukemia and lymphoproliferative disorders. *Am J Clin Pathol* 74:34–38, 1981
18. Mitsui H, Furitsu T, Dvorak AN, Irani AM, Schwartz LB, Inagaki N, Takei M, Ishizaka K, Zsebo KM, Gillis S, Ishizaka T: Development of human mast cells from umbilical cord blood cells by recombinant human and murine c-kit ligand. *Proc Natl Acad Sci USA* 90:735–739, 1993
19. Longley BJ, Morganroth GS, Tyrrell L, Dina TG, Anderson DM, Williams DE, Halaban R: Altered metabolism of mast cell–growth factor (c-kit ligand) in cutaneous mastocytosis. *N Engl J Med* 328:1302–1307, 1993